UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/403,844	04/18/95	FODSTAD	O	7885.33USWO

HM12/0525

MERCHANT GOULD SMITH EDELL
WELTER & SCHMIDT
3100 NORWEST CENTER
MINNEAPOLIS MN 55402

EXAMINER	
GABEL,G	
ART UNIT	**PAPER NUMBER**
1641	24

DATE MAILED: 05/25/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/403,844	Fodstad et al.
Examiner	**Group Art Unit**
Gailene R. Gabel	1641

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 3-12-99.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 25-28, 28, 29, 33-43, 46-48, 51, 59-62, 64, 66, 67-69, 71-75, 78-107 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 22-25, 28, 29, 33-40, 43, 46-48, 51, 59-62, 64, 66, 67, 69, 71, 72, 75, 78, 79, 87-89, 92, 93, 96, 101, 105-107 is/are rejected.

~~☐ Claim(s) _____ is/are objected to.~~ Continued

☒ Claim(s) 41, 42, 73, 74, 80-86, 90, 91, 94, 95, 97-100, 102-104 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892 ✓

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

Restriction/Election

1. Applicants' response to an election requirement in Paper No. 21 on March 1, 1999 is acknowledged and has been entered. Applicants elected ***counting*** as a method for characterizing separated cells, ***cancer antigens*** as the moiety to which antibody or fragment is directed against, and ***using an antibody or a fragment directed to an antigen expressed on a target cell*** as a method of detecting a target cell. Therefore, claims 41, 42, 73, 74, 80-86, 90, 91, 94, 95, 97-100, 102-104 have been withdrawn as claims directed to nonelected species. Currently, claims 22-25, 28, 29, 33-40, 46-48, 51, 59-62, 64, 66, 67, 69, 71, 72, 75, 78, 79, 87-89, 92, 93, 96, 101, 105-107 are pending.

Applicants argue that species election of methods for characterizing separated cells is not proper because they are not patentably distinct. Furthermore, applicants submit that it would not be overly burdensome to search each particular species on each group as set forth in the previous action in Paper No. 21 for election requirement. Examiner respectfully disagrees because each method for characterizing separated cells which includes counting of separated cells, analysis of DNA, mRNA, protein, PCR and cell culture growth requires different modes of operation and different effects rendering each species patentably distinct. Furthermore, the search required for one single species is not necessarily required for another species. Because these inventions are distinct for the reasons given above, election for examination purposes as indicated is proper.

Applicants are requested to note that literature search for each species from each group is distinct since the structural requirements of each species are different. While searches would be expected to overlap, there is no reason to expect the searches to be coextensive.

The election requirement set forth is deemed proper and is therefore made FINAL. Claims 41, 42, 73, 74, 80-86, 90, 91, 94, 95, 97, 98, 102 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejection of claims 29, 61, and 78-79 has been withdrawn in light of applicants' amendments to obviate a 112 second paragraph rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 22-25, 28, 29, 33, and 105 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. (EP 016,552) in view of Connelly et al. (U.S. Patent 5,422,277).

Widder et al. teach a method for separation of select population of cells from a mixed cell population using magnetic particles coated with a layer of specific antibodies which selectively bind to the select population. The coated microspheres with antibodies specific to target cells are contacted with the mixed population and the bound select population is magnetically separated from the mixed population (see page 4, last paragraph). The magnetically responsive microspheres have Protein A associated into the surface which selectively binds antibodies through the Fc region of the antibodies so that Fab arms of the antibodies extend outwardly for binding (see page 4, first paragraph). Widder et al. teach microspheres which are coupled with FITC conjugated rabbit IgG by incubation at 37°C for 20 minutes and examined (see page 10, Example 1). Furthermore, Widder et al. teach using the coated particles to separate red blood cells (RBC) from suspensions containing a mixture of different RBCs. Antibodies were coupled

to the microspheres by incubation of 0.5 mg of the microspheres suspended in 0.2 ml. of 0.9% NaCl solution containing 0.1% Tween 80 (polyethylene sorbitans monooleate). The RBCs were labeled with ^{51}Cr and incubated with mild agitation and bound microspheres were separated and counted using a gamma counter (see page 11, Example 2).

The method of Widder et al differs from the instant invention in failing to teach incubation of the antibody coated microspheres in mild detergent for 5-10 minutes to 2 hours at 4°C. Furthermore, Widder fails to teach the use of an antibody to immobilize antibodies on the surface of the magnetic particles.

Connelly et al. teach various fixatives used to fix cells without destroying cellular properties. Connelly et al. specifically teach fixing cells with phosphate buffer solution followed by DMSO and DNBS, Tween™ (polyethylene sorbitans monolaurate - Tween 20 or monooleate - Tween 80) and formaldehyde (see column 9, lines 10-14) and then incubating the cells for 20 minutes to 2 hours at temperatures ranging from 0°C to 37°C (see column 9, lines 20-48).

It would have been obvious to one of ordinary skill in the art to use antibodies to immobilize other antibodies on the surface of the magnetic particles in the method of Widder et al because such method of immobilizing antibodies on the surface of a solid support, such as magnetic particles is conventional and well known in the art. It would have been obvious to one of ordinary skill in the art to use detergents to treat cells as used by Connelly following certain specific temperature and time parameters because the use detergents to treat cells is well known and conventional in the art for removing extraneous matter from the cells that will interfere with

assays. One of ordinary skill in the art would have been motivated to incorporate Connelly's fixative techniques and parameters in Widders separation method because Connelly specifically states that one of ordinary skill in the art of cell fixation may routinely have to vary the aforementioned cell treatment parameters as in Widder's RBCs (dependent on cellular type) in order to obtain desired cell fixation without substantial destruction of cellular properties.

4. Claims 22, 34-40, 43, 48, 67, 69, 71, 72, 75, 87-89, 92, 93, 96, and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. in view of Kemmer et al. (Journal of Immunological Methods, 1992) and Holmes et al. (WO 91/09938) and in further view of Terasaki et al. (U.S. Patent 4,752,569).

Widder has been discussed supra.

The method of Widder et al differs from the instant invention in failing to teach separation and detection of specific cells, in this case, cancer cells.

Kemmer et al. teach isolation of tumor cells from a mixed cell suspension of human tumor tissue which contains tumor cells, leucocytes, and erythrocytes, using magnetic beads coated with monoclonal antibodies.

Terasaki et al. teach the preparation of monoclonal antibodies for use in the diagnosis of neoplastic conditions, with a wide variety of different tumors. The hybridoma producing the monoclonal antibodies (designated as CSLEX1) can also be used for transforming other cells to make them monoclonal antibody producing or as a source of the gene expression of the

immunoglobulin. The entire antibody need not be used but rather only fragments such as Fab, $(Fab')_2$, etc. Terasaki et al. teach incorporation of monoclonal antibodies into reagents for use in detection methods. The monoclonal antibodies may be labeled with enzyme such as horseradish peroxidase and conjugated covalently or non covalently with other antibodies or with magnetic particles for use in diagnostic assays. Table 2 enumerates a list of the reactivity of monoclonal antibody CSLEX1 against solid tumor cell lines by cytotoxicity/ Immunofluorescence/ Immunoperoxidase.

It would have been obvious to one of ordinary of ordinary skill in the art at the time of the instant invention to use the method of Widder et al to separate cells from a variety of cell samples, as taught by Kemmer et al because Kemmer et al teach that it is advantageous to remove tumor cells from a mixed cell suspension using magnetic microbeads coated with monoclonal antibodies or Protein A for the purpose of further studying the tumor cells or to purge a sample of tumor cells. The use of various monoclonal antibodies specific for neoplastic cell lines such as those taught by Terasaki et al. is well known in the art for specifically detecting specific antigens and a skilled artisan would have had a reasonable expectation of success in choosing a monoclonal antibody that is specific for an antigen on the surface of any cell population of interest.

5. Claims 22, 46-48, 51, 59-62, 64, 66, 67, 69, 71, 78, 79, 106, and 107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al. in view of Forrest et al. (U.S. Patent 4,659,678).

Widder has been discussed supra. The method of Widder et al. differs from the instant invention in failing to teach the use avidin-biotin system and a test kit.

Forrest et al teach a sandwich assay wherein a complex is formed between antigen in a sample and two or more antibody reagents and bound to solid supports such as magnetic or paramagnetic particles or beads having labeled or unlabeled antibodies attached thereto (see Abstract, column 1 and 2). The label employed may be selected from those known in the art such as fluorimetric or enzyme labeling. Forrest et al. teach using Protein A attached to the solid support and further attached to an antibody (see column 3-4). Forrest et al. teach using antibody reagents (which constitute intact antibodies or fragments thereof) that constitute a specific binding protein such as avidin and biotin and adding the reagents in any order so as to optimize the reaction conditions (column 5).

It would have been obvious to one of ordinary skill in the art to use a binding system such as avidin-biotin as taught by Forrest et al. in the method of Widder et al. because Forrest et al. teach that avidin-biotin provides a very rapid and high binding affinity which offers the advantage of a more accurate and rapid assay.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use a binding system used by Forrest et al in the method of Widder et al, as modified by Forrest et al in a test kit arrangement because test kits are conventional and well known in the art for their recognized advantages of convenience and economy.

Arguments and Traversals Re: Widder Reference

Applicants argue that there are numerous differences between the present invention and the disclosure of Widder et al. reference:

1. Widder et al. differs

from the instant invention in failing to teach the use of enzyme labels and an avidin-biotin system. Widder et al. does not teach using fixatives to pretreat sample. This argument is not persuasive because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Widder reference was combined with the pretreatment technique of Connelly reference and the avidin-biotin system and enzyme labeling of Forrest reference. One of ordinary skill in the art would have been motivated to incorporate Connelly's fixative techniques and parameters in Widders separation method and Forrest's detection method because Connelly specifically states that one of ordinary skill in the art of cell fixation may routinely have to vary the aforementioned cell treatment parameters as in Widder's RBCs (dependent on cellular type) in order to obtain desired cell fixation without substantial destruction of cellular properties.

2. Widder et al. only performed a coarse separation of blood cells, not detection of individual cells. This argument is not persuasive because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Widder separation method was combined with the method taught by Forrest et al. and monoclonal antibodies of Terasaki et al. in order to individually detect specific cancer cells. A skilled artisan would have had a reasonable expectation of success in choosing a monoclonal antibody that is specific for an antigen on the surface of any cell population of interest.

3. Widder et al. made particles with protein A embedded and that their particles are not uniform in size and amount of Protein A so that the amount of antibody per particle and exact orientation on the antibody is unknown. In response, one of ordinary skill in the art may routinely have to vary particle preparation parameters in order to obtain desired particle size and composition to achieve optimum results.

4. The content of iron in Widder's particles varies. Due to reasons aforementioned (2-4) the particles of Widder will adhere to non-target and target cells alike and the specificity of the method will be reduced. This argument is not persuasive because iron content is not recited in the claims. Refer to responses in 1, 2, 3, and 4 for adherence to non-target cells.

5. Protein A will show specific binding to B-cells and plasma cells, both of which are non-target cells according to the present method. Refer response in 2 for specific binding.

6. Widder's test system is simple and the magnetic strength of their particles is not powerful enough to pull a few target-cells out of a population of several million cells. This argument is not persuasive because magnetic capacities are not recited in the claims.

In response to the use of detergents to treat cells, Examiner remarks that the use of detergents is well known and conventional in the art for removing extraneous matter from the cells that will interfere with specificity in assays. Furthermore, Widder incubated 0.5 mg of microspheres in suspension in 0.2 ml. of 0.9% NaCl solution containing 0.1% Tween 80 (polyethylene sorbitans monooleate)(see Example 1). In incorporating therewith Connelly's incubation parameters within low temperature range which was proposed to vary between cells of interest, a required specificity as that of the instant invention can be achieved.

Applicants comments and arguments were considered but not persuasive. Therefore, no claims are allowed.

Remarks

Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

Ho (U.S. Patent 4,857,452) teach an assay for carcinoma of breast, colon and ovary.

Olsson (U.S. Patent 5,019,497) teach human squamous lung carcinoma cell specific antigens and antibodies.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

5/19/99

Gailene R. Gabel
Patent Examiner
Art Unit 1641

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641